A Regulatory Perspective on the Development of New Vaccines Against *Bacillus anthracis* and Lessons Learned Thus Far

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Anthrax Disease

Bacillus anthracis:

- Gram positive, spore forming bacterium
- Highly resistant spores

Natural Infection:

- Cattle, sheep, goats, wild game

Experimental Infection:

- Nonhuman primates, rabbits, mice, rats, guinea pigs

Human Disease:

- Cutaneous anthrax
- Gastrointestinal anthrax
- Inhalational anthrax

Bacillus anthracis

Virulence

- pX01– toxins
  - PA—protective antigen
  - LF—lethal factor
  - EF—edema factor
- pX02—capsule

Bacillus anthracis

LF + PA = Lethal Toxin

EF + PA = Edema Toxin

A-B toxins

- B domain—target cell binding, internalization & translocation
- A domain—cytotoxic domain

Anti-PA Antibodies: associated with protection against anthrax disease and disruption of cytotoxic pathway

PA = antigen of interest for vaccines

Anthrax Vaccines

US Licensed Vaccines

Human: BioThrax™ (Anthrax Vaccine Adsorbed)

- Protective Antigen (PA) Based Vaccine
- Active immunization against *Bacillus anthracis* of individuals between18 and 65 years of age...

Veterinary: Anthrax Spore Vaccine

- Nonencapsulated Live Culture
- Suspension of Viable Spores

Next Generation Anthrax Vaccines

- Highly purified recombinant proteins
  - Single or multivalent immunogens
- Viral or bacterial vectored vaccines
- DNA vaccines
- Others ?

Next Generation Anthrax Vaccines

Novel delivery systems

- Proteosomes, microsomes, liposomes

Novel adjuvants

- Inactivated toxins (CT, LT), chemical, lipid based

Nontraditional routes of administration

- Oral, intranasal, transdermal

CBER Regulatory Philosophy

Application of Regulatory Standards with consideration for …

- uniqueness of the product
- target population
- intended use
- evolving scientific knowledge

Stages of Review and Regulation In Vaccine Development:

Clinical Investigational Plan

IND

Phase 1
Safety,
Immuno-
gentility
(tens)

→

Phase 2
Safety,
Immuno-
genicity,
Dose –
Ranging
(hundreds)

→

Phase 3
Safety,
Immuno-
genicity,
Efficacy
(thousands)

→

BLA
Data to
support
approval;
Pre-
Approval
Inspection

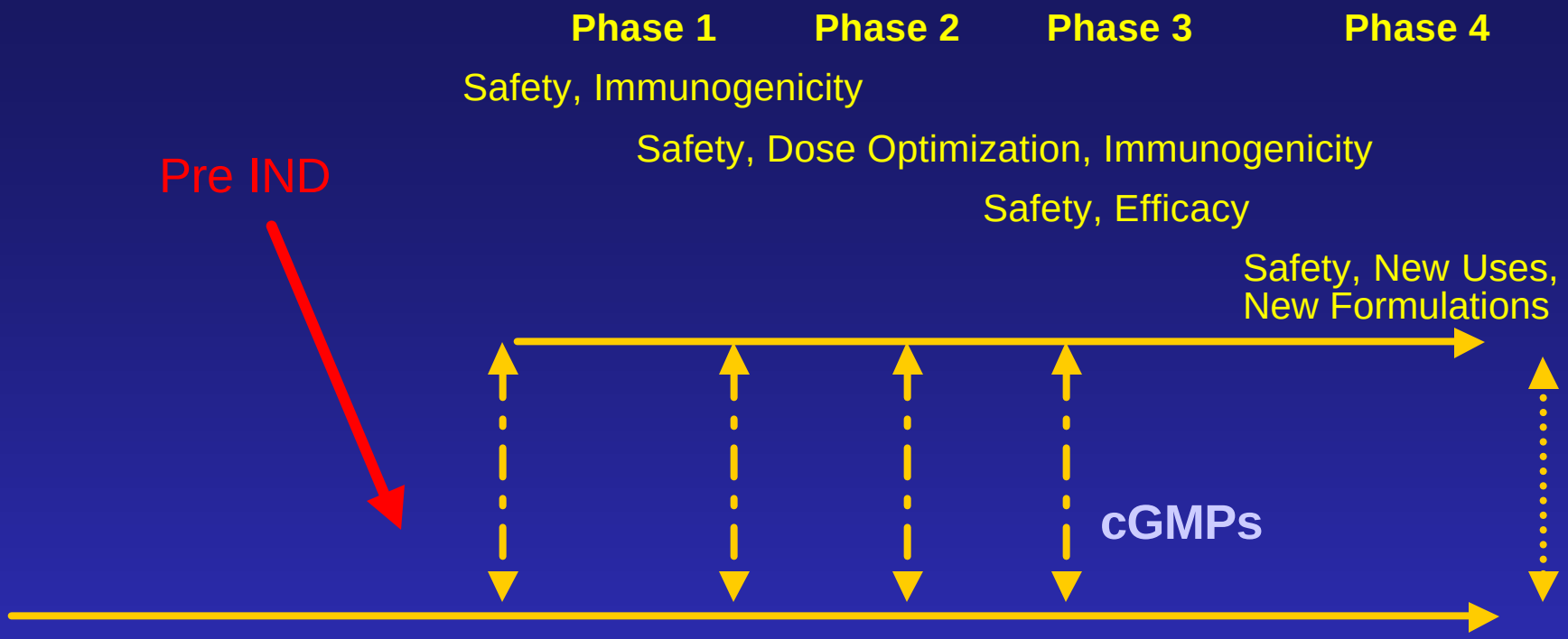
→

Phase 4
Inspection
Safety
Efficacy
Lot Release

→

BLA
Supplement
(Post-approval
Changes)
New Indications
Dosing
Manufacture
Equip./Facilities

Establishment of Manufacturing and Testing Controls, Specifications



Product ID, Characterization

Preclinical Safety and Immunogenicity

Optimization of Manufacturing Process

Process Validation

Assay Development & Assay Validation

Final Product Specifications

Final Formulation/Dosage

Manufacturing Changes

Formulation Changes

Biological Agents/Diseases

Category A:

- Anthrax (*Bacillus anthracis*)
- Botulism (*Clostridium botulinum* toxin)
- Plague (*Yersinia pestis*)
- Smallpox (variola major)
- Tularemia (*Francisella tularensis*)
- Viral hemorrhagic fevers (Ebola, Marburg, Lassa, Marchupo…)

Category B:

- Brucellosis (*Brucella species*)
- Epsilon toxin of *Clostridium perfringens*
- Food Safety Threats (*Salmonella* sps, *E. coli* 0157:H7, Shigella)
- Glanders (*Burkholderia mallei*)
- Melioidosis (*Burholderia pseudomallei*)
- Psittacosis (*Chlamydia psittaci*)
- Q fever (*Coxiella burnetii*)
- Ricin toxin from *Ricinus communis*
- Staphylococcal enterotoxin B
- Typhyus fever (*Rickettsia prowazekii*)
- Viral encephalitis (VEE, EEE, WEE)
- Water Safety Threats (*Vibrio cholerae*, *Cryptosporidium parvum*)

Demonstration of efficacy via the Animal Rule…

… means an additional development program (animal efficacy model) to be conducted in parallel with the clinical and manufacturing programs…..

Animal Model Considerations

Identification of appropriate animal species

- Experimental infection
- Pathophysiology of the disease
  - Time to onset of symptoms
  - Nature of symptoms
  - Time to death
  - Effects of agent challenge dose and route of exposure on morbidity and mortality

Animal Model Considerations

Identification of appropriate animal species (cont.)

- Immune response to vaccine
  - Antibody response
  - Cell mediated immune response
  - Kinetics of response

Animal Model Considerations

Identification of appropriate animal species (cont.)

- Proof-of-Concept studies:
  - Dose ranging
  - Schedules of administration
  - Challenge-protection studies
  - Initial demonstration of a protective level of response or protective threshold
  - Insight on selection of human doses and immunization schedules

Animal Model Considerations

Efficacy Study Design Considerations

- Dose/schedule optimization to elicit response reflective of human immune response to vaccine
- Immunogenicity endpoints (assays, kinetics, duration, correlates)
- Efficacy endpoints (morbidity, mortality)
- Challenge doses
- Route of exposure
- Concomitant Therapies

Animal Model Considerations

Bridging Animal Efficacy and Human Trails

- Extrapolation of animal model protective level as a predictor of human protection

  - Bridging/Correlating animal and human clinical immunogenicity assays
  - Passive (human-to-animal) immunization-challenge studies

Animal Models:

Efficacy Studies

Phase 1 Phase 2 Phase 3 Phase 4

Dose/Schedule Optimization

Immunogenicity (assays, kinetics, duration, correlate)

Challenge doses & route of exposure

Efficacy Endpoints

Concomitant Therapies

Safety, Immunogenicity

Safety, Dose Optimization, Immunogenicity

Safety, Efficacy

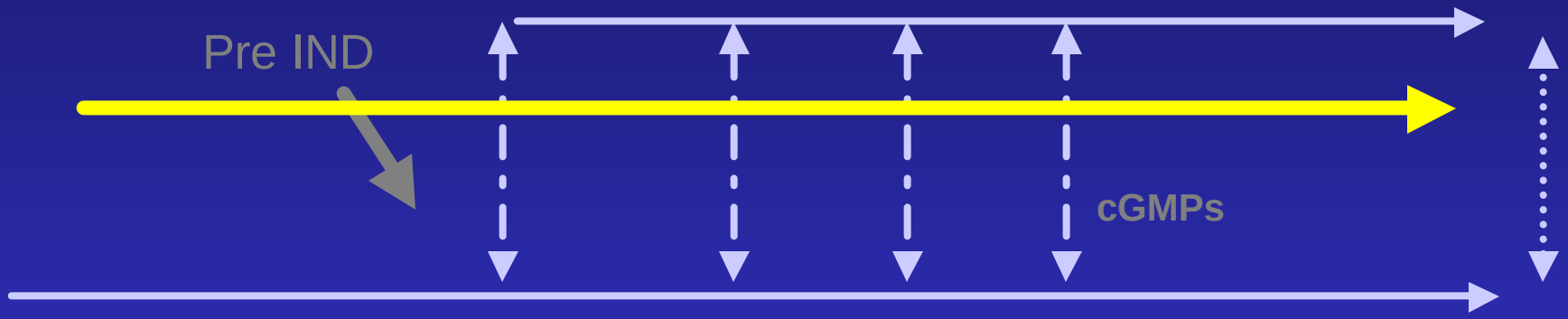
Safety, New Uses, New Formulations

Species Identification

Pathology

Immunogenicity

"Proof-of-Concept"



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Bridge to Human Trials

Immunogenicity

Dose/Schedule

Resources

Facilities

Staff

Animals

Clinical Indication

Vaccines, traditionally, are intended for prophylaxis in a pre-exposure setting.

From a counter-terrorism perspective, however, both pre-exposure and post-exposure prophylaxis clinical indications may be desired.

Clinical Indication

Pre-exposure & Post-exposure prophylaxis

- Presumed differences in optimal vaccination schedules for these scenarios
- Human immunogenicity data
- Human safety data

Clinical Indication

Pre-exposure & Post-exposure prophylaxis

- Animal model efficacy studies to support each indication
  - Post-exposure study considerations
    - Time to treatment after challenge
    - Challenge dose
    - Concomitant therapies
    - Immunogenicity & Efficacy Endpoints

Clinical Indication

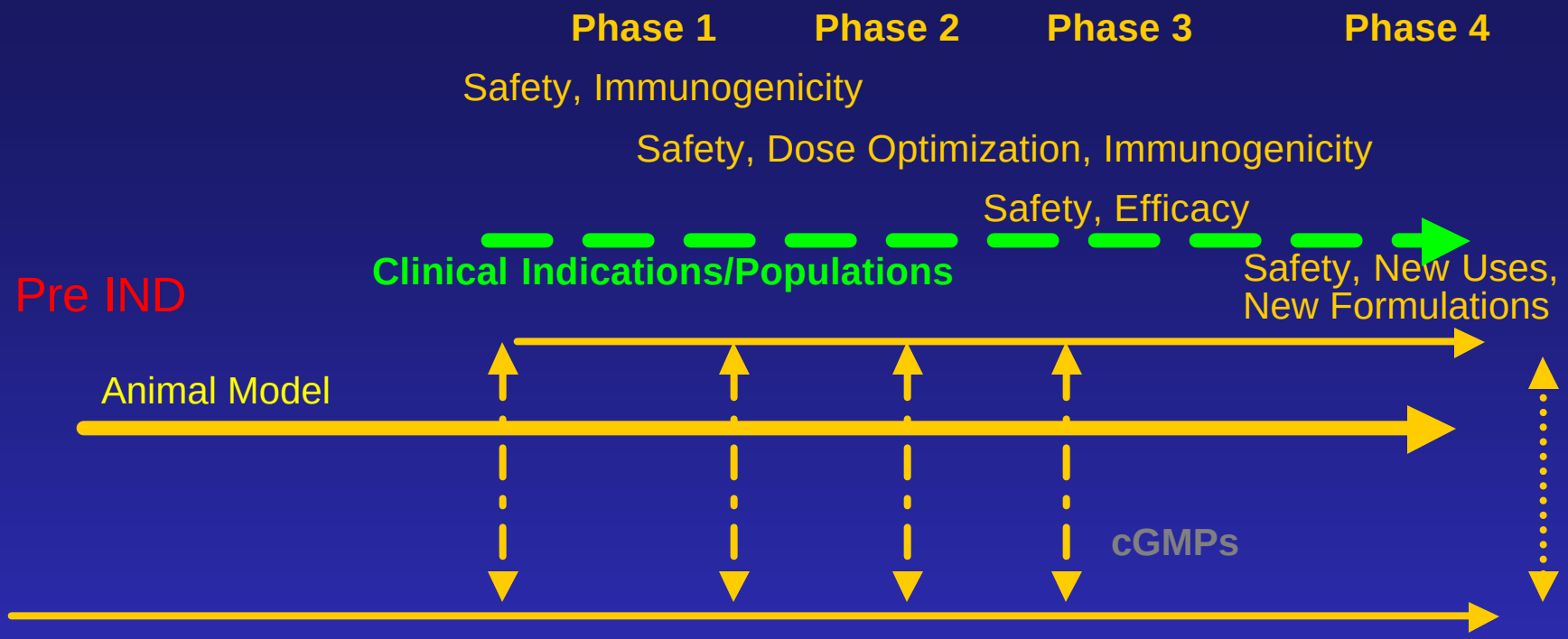
Intended or Target Patient Population

- Healthy adults
- Pediatric populations
- Geriatric populations
- Other considerations
  - Immunosuppressed/Immunocompromised
  - Pregnancy

Clinical Indication

Intended or Target Patient Population(s)

- Safety
- Immunogenicity
- Bridge to Efficacy



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Stockpile Considerations

Product stability

- Shelf-life and supply rotation
- Product Formulation
  - Preservatives
  - Excipients & Stabilizers

Preclinical data

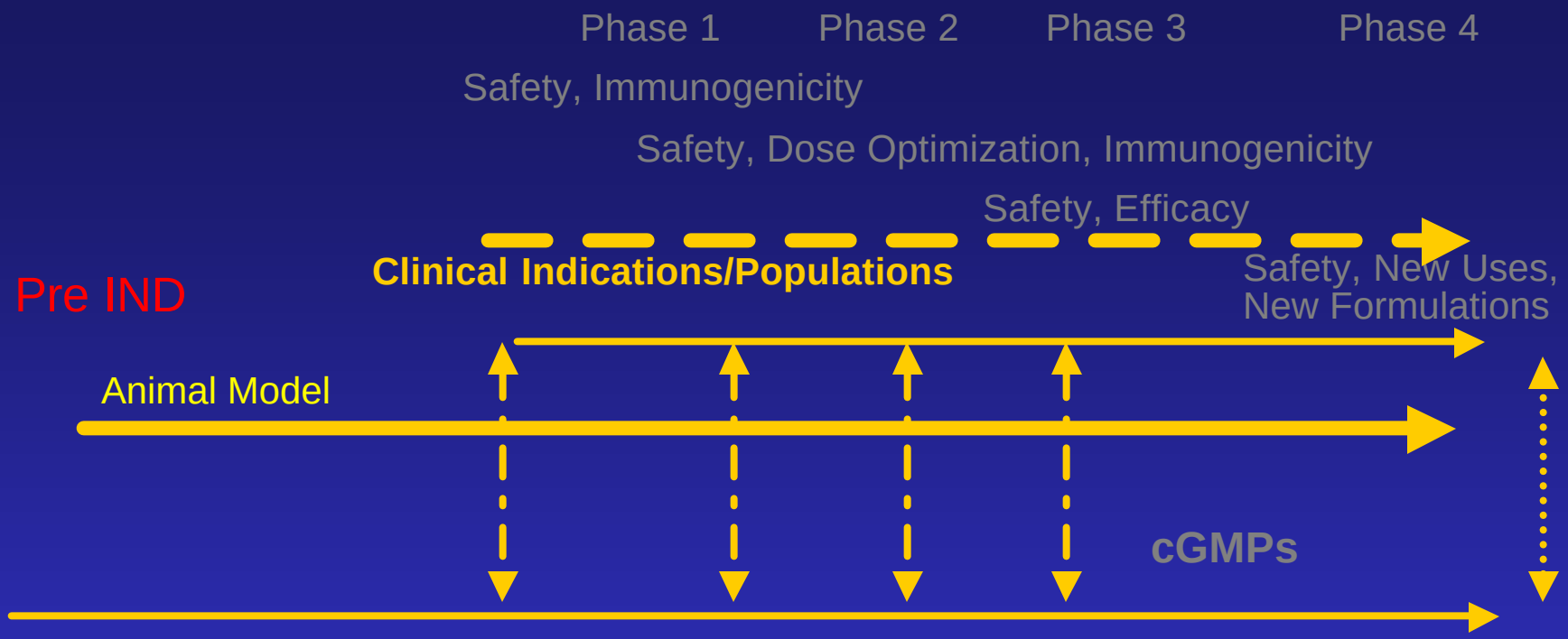
Manufacturing/product testing data

Clinical data

Stockpile Considerations

Product Packaging/Presentation

- Multidose vs Single dose presentation
- Delivery system
  - Injection:
    - solution vs. lyophilized powder w/ diluent
  - Oral
  - Transdermal
  - ??



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Stockpile Considerations

stability/formulation/presentation…

Optimization of Manufacturing Process

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Potential Availability under IND

Data to support IND use

- Preclinical Safety
- Human Immunogenicity
  - Dose/Schedule
- Human Safety
  - Dose/Schedule
- Effectiveness/Protection in Animal Model
  - Not necessarily pivotal Animal Rule Study

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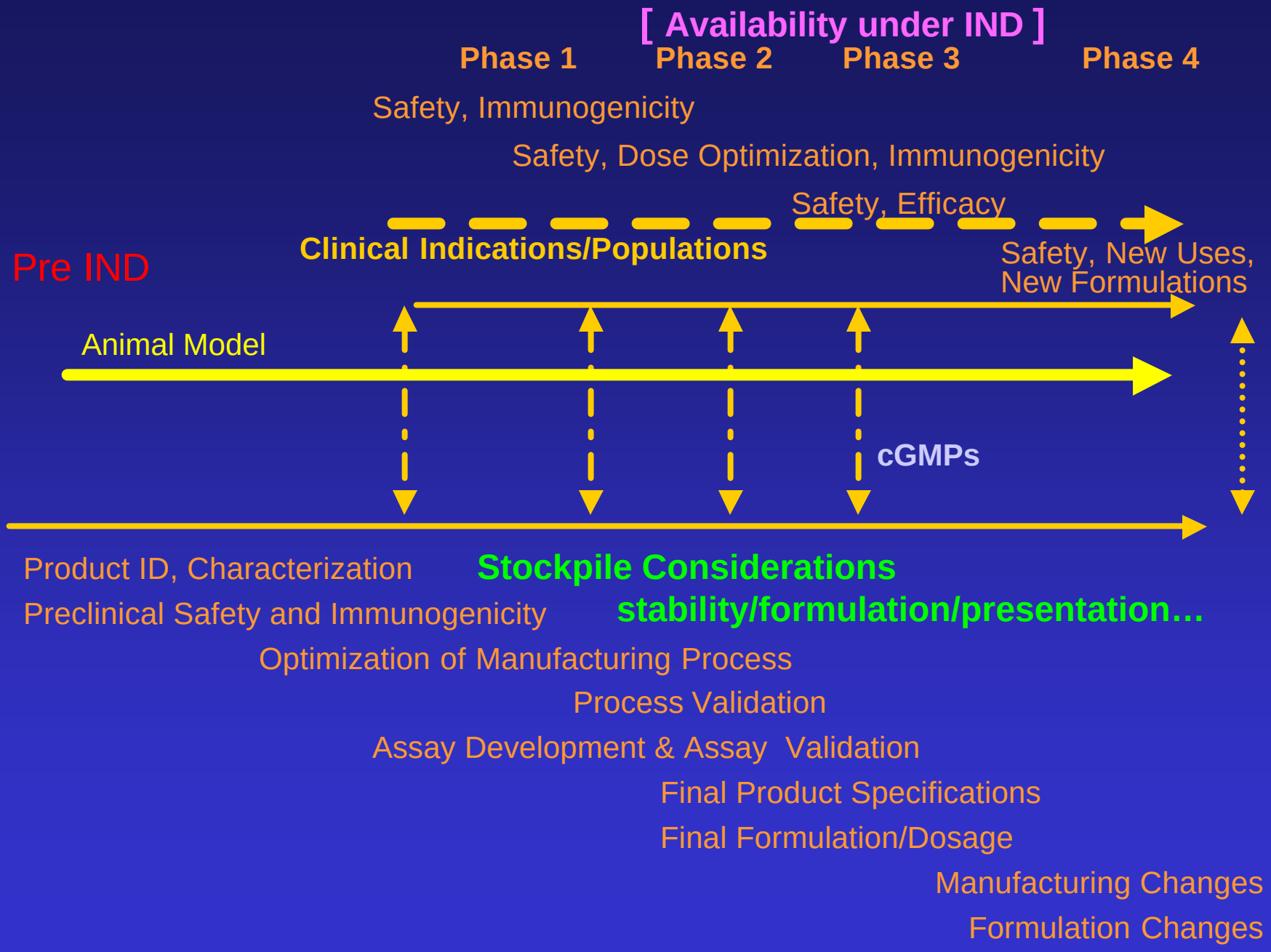
[Availability under IND]
Phase 1
Phase 2
Phase 3
Phase 4
Safety, Immunogenicity
Safety, Dose Optimization, Immunogenicity
Safety, Efficacy
Clinical Indications/Populations
Safety, New Uses,
New Formulations
Pre IND
Animal Model
cGMPs
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Perceived sense of urgency and/or expectation for condensed development timeframes places an even greater importance on…

- Careful attention to detail and application of sound scientific principles at even the earliest points in development.
- Pre-IND activities
  - Antigen identification/characterization
  - Disease pathophysiology in humans and experimental animal models
  - Mechanisms of vaccine protection
- Foundation for product, clinical and animal model development programs

Facilitation of development programs….

- Frequent and early communication
- Open communication channels
  - Early disclosure of complications can promote problem-solving collaborations
- Incorporate CBER advice points or provide alternative approaches and sound scientific rationale

Facilitation of development programs….

- Seek input from experts in academic and medical communities
- CBER Guidance to Industry and Points-to-Consider Documents
- International Committee on Harmonization Guidance Documents
- Workshops: announcements, summaries, slide presentations

  www.fda.gov/cber/reading.htm

Acknowledgments

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Director

Division of Vaccines and Related Products Applications
OVRR/CBER

Colleagues in…

Division of Vaccines and Related Products Applications

Division of Bacterial, Parasitic and Allergenic Products

Division of Manufacturing and Product Quality